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## Ideal Vial Size for Bortezomib: Real-World Data on Waste and Cost Reduction in Treatment of Multiple Myeloma in Brazil

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### ABSTRACT

**Objectives:** Single-size vials of drugs may be a source of waste and increase in treatment costs. Bortezomib, indicated for multiple myeloma (MM) treatment, is available in 3.5-mg vials, a quantity higher than the average dose commonly prescribed. This analysis aimed to demonstrate, through real-world data, which would be the optimal vial presentation for bortezomib in Brazil and quantify the reduction in medication waste related to this option. **Methods:** From November 2007 to October 2009 all patients with MM treated with bortezomib were identified via the Evidências database. Analysis of prescribed, dispensed, and wasted doses, their costs and projections of the ideal vial size were performed. **Results:** Thirty-five patients (mean body surface area of 1.73 m<sup>2</sup>) received 509 infusions in 131 cycles of treatment (average of 3.77 cycles per patient). The average dose prescribed was 2.1 mg per infusion (95% confidence interval [CI] 1.97–2.26) with average

waste of 39.5% of the vial content (95% CI 35.35–43.76). The mean waste per patient per day was 1.38 mg (95% CI 1.24–1.52). If a 3-mg vial were available, the average drug waste per patient per day would be 0.88 mg (95% CI 0.74–1.03) or 36.2% less. With a 2.5-mg vial the waste would be 1.05 mg (95% CI 0.81–1.29) or 23.9% less. If two presentations were available (2.5 mg and 0.5 mg), the waste would be 0.52 mg (95% CI 0.4–0.63) or 62.5% less. Considering the price of the different vials to be proportional to the original 3.5-mg vial, the cost would be also reduced by the same rates described above. **Conclusions:** A simple adjustment in vial size may reduce the waste of bortezomib by 36% to 62% and can also reduce the cost of treatment.

**Keywords:** bortezomib, cost-reduction, drug waste, myeloma.

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### Introduction

Multiple myeloma (MM) is considered a chronic disease for which—despite many advances in therapy—there is currently no curative treatment available. The development of novel agents that target the tumor cell and the microenvironment, immunomodulators, proteasome inhibitors, and bisphosphonates has changed the standards of care for affected patients. Even with the achievement of complete responses in few cases, the ultimate goals for patients with MM are extended survival and quality of life [1–4].

The costs associated with current and emerging therapies, as well as supportive care, are significant and pose a tremendous financial burden to both patients and health care systems [5]. This is an important aspect to be considered, especially in underdeveloped countries and emerging economies in which the bulk of resources destined to health care is often reduced and unevenly distributed.

Newer classes of cytotoxic agents are, for the most part, very expensive and there may be considerable resource savings in the judicious application of dose rounding without any negative clinical effect, given the significant interpatient pharmacokinetics and pharmacodynamics variability for most cytotoxic drugs [6]. Single-size vials of chemotherapy drugs may be an undernoticed source of waste and increase in treatment costs. There is, however, the possibility of customizing the dose of chemotherapy for

each patient not only by the body surface area (BSA) measurement, but also by adjusting the final dose to the nearest vial size. Previous published studies described this kind of adjustment as cost saving in several types of chemotherapy treatments [6,7].

Bortezomib (Velcade, Janssen-Cilag, Beerse, Antwerp, Belgium) is a drug frequently used in MM treatment that is available in Brazil and in many other countries only as a 3.5-mg vial. This presentation dose is higher than the average dose commonly prescribed and due to the lack of preservatives in the vial, it is mandatory that the drug be administered within 8 hours of preparation. This analysis aimed to demonstrate, through real-world data, which would be the optimal vial presentation for bortezomib in Brazil and to quantify the reduction in medication waste and costs related to it.

### Study design

This study is a retrospective analysis of data extracted from Evidências Database (ED), an electronic system design to evaluate chemotherapy requests from health care providers and permit the approval or denial of coverage by auditors. The database is available as a secure Web site where patient data such as age, disease stage, BSA, and drugs requested among other information are prospectively stored. ED covers approximately 5% of the Brazilian pri-

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vate health care market. For this analysis we used the payer's perspective on the private health care system.

During the period of November 2007 to October 2009, all patients diagnosed with MM (cases entered into ED with the International Statistical Classification of Diseases and Related Health Problems code C90.0), submitted to treatment containing bortezomib for at least one infusion were identified. All patients were treated in private care referral cancer centers, according to usual chemotherapy protocols and identified on the auditing medical system.

Details regarding the prescribed dose of bortezomib, individually and collectively wasted doses, and the respective average doses per patient and per cycle were retrieved. The actual dose dispensed to perform the infusion was also calculated. That is important because it is often necessary to open multiple vials to fulfill the prescribed dose, thus accounting for increased waste.

The costs of the wasted drug and the projection of costs saved with different vial sizes were calculated.

The mean and average calculations were performed based on usual mathematical formulas and were represented as milligrams, US dollars, the Brazilian currency reals (R\$), or square meters, according to the variable studied. The results are reported with the corresponding 95% confidence interval (CI). The amount of drug wasted was also expressed in percentage related to the total content of the 3.5-mg vial. The results of costs were expressed in US dollars with the cost of the 3.5-mg bortezomib vial being R\$4218.33 or US\$2343.51 (exchange rate R\$1.80 to US\$1 as of May 2010). The price list used was the Brazilian Official Price List [8], determined by the federal government, by the wholesale price plus taxes. Differently sized vials were priced proportionally to the existing vial for economic projections.

No patient was identified by name or any particular characteristic during this study. All health care providers previously authorized the data extraction in signed contracts. Because the purpose of this study was to evaluate the optimal presentation for bortezomib, the clinical aspects and the outcomes regarding effectiveness and security of this drug were not taken into consideration.

## Results

Thirty-five patients with MM treated with bortezomib (alone or in association with other cytotoxic drugs) were identified on ED. The mean body surface area was 1.73 m<sup>2</sup>. The average prescribed dose per infusion was 2.1 mg (95% CI 1.97–2.26) with average waste of 39.5% of the vial content (95% CI 35.35–43.76) of the contents of a standard 3.5-mg vial per day or 5.39 mg per cycle. The patients received a total of 509 days of infusion distributed in 131 cycles of treatment (average of 3.77 cycles per patient).

During the period of time analyzed, a total of 1781.5 mg were dispensed to cover 1075.7 mg prescribed, resulting in a gross loss of 705.7 mg (39.6%) of bortezomib. That means that of the US\$1,192,841.50 spent on the drug, US\$472,365.23 was wasted. The total amount of resource wasted per day, with all 35 patients, was US\$121,420.95. Those data are described in Tables 1 and 2 in the Supplemental Materials found at: [doi:10.1016/j.jval.2011.05.013](https://doi.org/10.1016/j.jval.2011.05.013).

The average waste projections for every patient per day and per cycle of treatment, respectively, according with the different vial sizes proposed is described in Table 2 (in Supplemental Materials found at: [doi:10.1016/j.jval.2011.05.013](https://doi.org/10.1016/j.jval.2011.05.013)). The percentage is defined in regard to the standard 3.5-mg vial. For a 3-mg vial, 0.88 mg/day (95% CI 0.74–1.03) or 36.2% less and 3.44 per cycle (95% CI 2.85–4.04). For a 2.5-mg vial, 1.05 mg/day (95% CI 0.81–1.29) or 23.9% less and 4.06 mg per cycle (24.6% more than with the 3.5-mg vial).

If two different presentations were available, 2.5 mg and 0.5 mg, the waste per patient per day would be 0.52 mg (95% CI 0.4–0.63) or 62.5% less and 2.01 mg/per cycle (62.7% less than with 3.5-mg vial).

The cost reduction projections per day and per cycle, respectively, assuming a proportional price of the proposed vials to the 3.5-mg vial, are described in Table 3 in the Supplemental Materials found at: [doi:10.1016/j.jval.2011.05.013](https://doi.org/10.1016/j.jval.2011.05.013).

Using the currently available 3.5-mg vial, an average of US\$926.88/day and US\$3,607.33/cycle are lost. If a 3-mg vial were available, the average loss would be US\$592.09/day (36.1% less than with the 3.5-mg vial size) and US\$2306.51/cycle.

With the 2.5-mg vial, the average waste per patient per day was US\$704.54 (23.9% less than with the 3.5 mg vial size but 15.9% higher than with the 3-mg vial size) and \$2717.97 per cycle.

If considering the combination of 2.5-mg plus 0.5-mg vials sizes, the loss would be US\$346.75/day (62.5% less than with the 3.5-mg vial size) and US\$1348.15 per cycle (62.6% less). The total cost wasted per day for all 35 patients was US\$45,424.01 (62.5% less than with the 3.5-mg vial size) or US\$176,607.25 per cycle.

## Discussion

Although MM accounts for only a small percentage of all cancers, the costs associated with treating and managing it are among the highest [9]. Recent developments in diagnosing, treating, and managing MM have led to novel treatment strategies. Immunomodulators, proteasome inhibitors, and bisphosphonates are improving response rates and preserving patients' quality of life [10]; however, these agents are not replacing the older treatment modalities, but rather being used in addition to them [11].

The landscape of myeloma therapy has changed radically since 1999 with the introduction of new therapies and better prognostic indicators ushering in a new era of MM management [10]. Novel agents resulting in extended survival and better understanding of the biology of the disease have helped select patients most likely to benefit from stem cell transplantation. The costs associated with current and emerging therapies, as well as supportive care are significant and likely to increase further on, as patients begin to live longer [5].

Furthermore, the majority of cytotoxic chemotherapy protocols are based on dosage calculation from BSA. There is a growing body of evidence that demonstrates the large interpatient variability associated with dosing by BSA [12–16]. Despite this known variability, it is common practice for clinicians to calculate doses of chemotherapy to the nearest milligram based on BSA estimated to two decimal points [12]. In some instances dose rounding is employed by the clinician (e.g., capping) and in others by pharmacists preparing the drug, but this is still more the exception than the rule [12]. There are practical implications related with costs and unnecessary losses in preparing cytotoxic doses calculated to the exact milligram.

Mertens et al. [11] conducted a study aimed to evaluate the effects of dose rounding on treatment cost. During the study period, 18 different anticancer drugs were administered 939 times. If dosage had been based strictly on BSA, drug costs would have been €509,664. Rounding off to whole ampoules with a dose margin of a maximum of 10% would have cost €465,619; a reduction of 8.6%. The rational application of the dose individualization principle based on body surface area may result in a substantial reduction in expenditure on anticancer drugs [11].

Dose rounding has been considered acceptable to within 5% of calculated dose because on the basis of pharmacokinetic and clinical issues this dose adjustment is not expected to have any significant effect on either response or toxicity [6,17–19].

Another possibility to help solve the waste problem would be to combine multiple infusions on the same day. In terms of our study, however, it would be highly unlikely, not only because of the rarity of the disease but also due to the fact that the 35 patients were located in 10 different states in Brazil.

The reason we assigned a proportional cost to the different bortezomib vials was because usually drug prices in Brazil are calculated to be proportional to their dosage; that is, if a medication is available in 50- and 100-mg vials, the latter will be twice as expensive as the former [8].

Drug waste may be defined as the consequence of an inappropriate disposal of unused or partially used ampoules, vials, or syringes of drugs [20]. It has been previously demonstrated that inefficiency of drug use and waste production may lead to a distinct economic loss, though experiences are limited and most studies are dated or focus on other therapeutic areas [9,20–22]. Decreasing waste is an attractive cost-cutting strategy because it neither limits specific drug use nor affects quality of care [7].

One of the main reasons for drug waste was essentially the limited extent of chemotherapy medication shelf-life and the narrow availability of a range of vial sizes flexibly matching with possible drug dosages [7]. Adopted corrective measures were the logical consequence of these findings: if drug instability is a basis for drug waste, it is reasonable to use, whenever possible, multidose vials that retain a much longer microbial and chemical stability and to operate a per pathology/per drug distribution system of chemotherapy sessions over the week to allow the reuse of leftovers in other patients while respecting drug stability [7].

One of the limitations of this study was its small sample size. Although we used a database that covers 5% of the Brazilian private health care market, MM is much less frequent than other neoplasms such as breast or colon cancer and therefore it is important that these findings are confirmed in larger cohorts of patients.

Finally, there has been much discussion on the rising prices of oncologic treatments and how much is too much [23]. We believe that this discussion is even more important in developing countries, which are plagued by a perennially insufficient health care budget. To keep the discussion active we made this analysis and intended to show how the simple adjustment of vial size in bortezomib could affect costs and minimize drug waste.

## Conclusions

A simple adjustment in vial size from 3.5 to 3.0 mg reduces bortezomib waste by 36%. If presentations of 2.5 mg and 0.5 mg were available, the waste reduction could be as high as 62%.

## Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at [doi:10.1016/j.jval.2011.05.013](https://doi.org/10.1016/j.jval.2011.05.013), or if hard copy of article, at [www.valueinhealthjournal.com/issues](http://www.valueinhealthjournal.com/issues) (select volume, issue, and article).

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